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February 8, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: Docket No. 01D-0489, FDA Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (66 *Federal Register* 224, November 20, 2001, pages 58151-58153)

Dear Madam/Sir:

Genentech is pleased to have the opportunity to offer comments on the Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees. We applaud the Food and Drug Administration in its efforts to assist sponsors of clinical trials in determining when a data monitoring committee is needed for optimal study monitoring and how such committees should operate. We have included the following comments on the draft document in an effort to support FDA in this endeavor.

General comments:

1. The guidance implies that the study is blinded. It should be more specific and state that the independence of the DMC is more relevant to blinded trials.

2. For large 'sponsor organizations', the infrastructure is such that there can be a group within the organization, but independent of the clinical team and the staff, responsible for decisions regarding the project. In this case, the guidance may be targeted to the project team rather than to the entire sponsor organization.

3. The DMC should review unblinded data. This should be emphasized more.

Comments on Specific Sections:

2. Determining need for a DMC

Change...*DMCs have generally been established for large, randomized multisite, studies that evaluate interventions...*

To...DMCs have generally been established for large, randomized multisite, blinded studies that evaluate interventions...

3.2. Clinical Trial Steering Committees

Change...*A Steering Committee, when it exists, has primary responsibility...*

To...A Steering Committee, when it exists, may have responsibility...

3.5. Others with Monitoring Responsiblities

Add to the end of the paragraph...FDA, in turn, is responsible for ongoing consideration of adverse experience reports from all trials of a given product. The sponsor may also establish an oversight group, outside the project team, who interacts with the DMC, reviews and accepts/rejects the recommendations, and is not involved in trial monitoring.

4.2. Confidentiality of Interim Data and Analyses

Change...*Knowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial; ... Sponsors should establish procedures to ensure the confidentiality of the interim data (see Section 4.3.1.4.).*

To...For blinded trials, knowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial; ... Sponsors should establish procedures to ensure the confidentiality of the interim data (see Section 4.3.1.4.). This is not necessary for open-label trials.

4.2.1. Interim Data

Add to the end of the paragraph...They should, however, work with the statistician who will be preparing and presenting the interim analyses prior to the first ananlysis of unblended data to develop a template for the interim reports. Some or all members of the independent entity may be within the sponsor organization if there are established procedures to safeguard the unblinded data from the project team and investigators.

4.3. Establishing Standard Operating Procedures

Change...*4.3. Establishing Standard Operating Procedures*

...The sponsor may draft these SOPs and present them to the DMC for agreement, or the DMC may draft the SOPs... The sponsor should submit a description of the SOPs to FDA well in advance of the performance of any interim analyses, optimally before the initiation of the trial.

To...4.3. Establishing guidelines for roles and functions of the DMC

...The sponsor should have an SOP for establishing a DMC and for defining a charter for each DMC. Because the role of a DMC may be different for every study, each DMC should have a well-defined charter that describes the specific study DMC's responsibilities, sponsor interactions and communication plans. The sponsor may draft these charters and present them to the DMC for agreement, or the DMC may draft the charter... The sponsor may submit a description of the charter to FDA well in advance of the performance of any interim analyses, optimally before the initiation of the trial.

4.3.1. Considerations for Standard Operating Procedures

Change...*4.3.1. Considerations for the Standard Operating Procedures*

To...4.3.1. Considerations for the DMC Charter

4.3.1.4 Format of Interim Reports to the DMC and Use of Treatment Codes

Add to the end of the first paragraph...The statistician preparing the reports to the DMC should ideally be independent of the sponsor and clinical investigators (and a Steering Committee if there is one) to avoid inadvertent influence of data trends on the conduct of the trial (see Section 6.3 and Section 6.4). In the event that the reporting statistician is within the sponsor organization, the statistician should be independent of the project team.

4.4 Potential DMC Responsibilities

Add new subsection...4.4.X. Open Label Studies

DMCs may also be useful for certain types of open label studies. As in Phase I and II studies, an external group overseeing efficacy and safety may be valuable when risk to participants appears unusually high, and when a DMC could provide additional, independent oversight. Since the investigators and sponsor know accumulating results, issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting.

4.4.1.5 Studies of Less Serious Outcomes

We feel this section is general in nature and does not specifically relate to DMCs. We recommend for this section to be deleted.

6.3. Risks of Sponsor Exposure to Interim Comparative Data

Add to the end of the first paragraph...However, even when unblinding is limited to a small group or a single individual within the sponsoring organization who do maintain confidentiality of the results, it should be appreciated that an individual with knowledge of interim data may reveal, or be perceived to reveal, information even inadvertently, e.g., by facial expression or body language. The risk may be lessened by ensuring that the individual with knowledge of unblinded data does not participate in decisions pertaining to the conduct of the study.

6.4. Conduct of the Interim Analysis

Add to the end of the paragraph...In any case, the statistician should have no responsibility for the management of the trial and should have minimal contact with those who have such involvement. The sponsor should have an SOP in place defining the role of this statistician and the infrastructure in place to keep him/her independent of the study.

6.5. Sponsor Access to Interim Data for Planning Purposes

Add to the bulleted section...• The sponsor should finalize the interim analysis plan prior to performing the interim analysis.

We hope that you find these comments useful as you are reviewing this draft guidance. We look forward to the publication of the final rule.

Sincerely,

Robert Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality and Compliance

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